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Increasing Sensor Flexibility Through Neuromodulation

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Abstract. Both biological and man-made motor control networks require input from sensors to allow for modification of the motor program. Real sensory neurons are more flexible than typical robotic sensors because they are dynamic rather than static. The membrane properties of neurons and hence their excitability can be modified by the presence of neuromodulatory substances. In the case of a sensory neuron, this can change, in a functionally significant way, the code used to describe a stimulus. For instance, extension of the neuron's dynamic range or modification of its filtering characteristics can result. This flexibility has an apparent cost. The code used may be situation-dependent and hence difficult to interpret. To address this issue and to understand how neuromodulation is used effectively in a motor control network, I am studying the GPR2 stretch receptor in the crustacean stomatogastric nervous system. Several different neuromodulatory substances can modify its encoding properties. Comparisons of physiological and anatomical evidence suggest that neuromodulation can be effected both by GPR2 itself and by other neurons in the network. These results suggest that the analog of neuromodulation might be useful for improving sensor performance in an artificial motor control system.

Introduction

Many forms of locomotion in both invertebrates and vertebrates result from the activity of central pattern generator (CPG) networks of neurons (see review by Marder and Calabrese [1996]). CPGs produce rhythmic motor patterns by virtue of the intrinsic properties of the neurons and the connections between them, even when disconnected from sensory afferents (Wilson, 1961). Sensory feedback, however, is usually essential for modifying the details of the basic rhythm to shape a physiologically relevant output in response to particular environmental or body conditions (Grillner and Wallen, 1977; Foth and Graham, 1983a,b; Pearson *et al.*, 1983).

Man-made CPG networks are used to generate movement in biologically inspired robots, as reflected in the papers in this collection (CASSLS, 2001). An artificial CPG has both the power and limitations of a biological one: it has a built-in robustness, but if there is to be flexibility in its output, it too will require input from sensors. The sensors employed in many robots differ from biological sensory neurons in a fundamental way. A typical man-made sensor is static. It always gives the same unambiguous response to a particular stimulus. Real sensory neurons are dynamic. The spike trains they generate depend not solely on the stimulus but also can be influenced by other factors. One of these factors is the presence of neuromodulators, substances that modify a neuron's membrane properties and hence its excitability (Kaczmarek and Levitan, 1987). Neuromodulation affects neurons in the sensory, central, and motor systems. In the case of a sensory neuron, neuromodulation can modify the spike train generated in response to a particular sensory stimulus. This can have functional significance. For example, when primary olfactory receptors in the newt are exposed to micromolar concentrations of adrenaline, the receptor's threshold for and differential sensitivity to odor perception are affected (Kawai *et al.*, 1999). This modulation may very well be crucial for an animal trying to find a mate or avoid becoming a meal.

The fact that sensory neurons can be modulated prompts an interesting line of questioning. Two distinct stimuli pre-

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sented in two different neuromodulatory environments could quite conceivably result in very similar spike trains. Does that imply that the meaning of the spike train is ill-defined? How might what appears to be ambiguity in the code be removed? In particular, how can sensor modulation be used to advantage in a CPG network?

The crab stomatogastric nervous system (STNS) is an ideal preparation in which to address some of these questions. The STNS controls the movements of stomach muscles used to grind and filter food and is today probably the most carefully studied and best understood small CPG network. Gastropyloric receptor 2 (GPR2) is a stretch-sensitive neuron that monitors the movement of two stomach muscles (Katz *et al.*, 1989) and provides this information to the CPG. There are several reasons why GPR2 is an attractive candidate for studying the computational significance of neuromodulation. (1) The stimulus (muscle tension) is well defined and one-dimensional (Katz *et al.*, 1989). (2) The neuron's response to muscle stretch can be modulated in several different ways, as will be described below. (3) The synaptic targets of GPR2 are known and accessible (Katz and Harris-Warrick, 1989, 1990), and signal processing of the sensory information can be investigated directly. The results discussed below imply that neuromodulation of GPR2 may allow the neuron to interact both with the stimulus environment and the central nervous system so that it can remain sensitive to important stimuli. Our investigations suggest that incorporation of the analog of neuromodulation into a robotic nervous system might similarly be useful for introducing dynamics to sensors to increase their functionality.

All experiments were done using male *Cancer borealis* crabs purchased from local seafood suppliers in Boston, Massachusetts. From the gut of the crab, a preparation consisting of two muscles and the nerve containing the GPR2 cell body was removed, placed flat in 5-ml silicone elastomer-coated petri dishes and continuously superfused with cooled physiological saline. One side of the *cpv3a* muscle (nomenclature from Maynard and Dando [1974]) was pinned to the dish. The other side was attached to a force-displacement transducer. This transducer in turn was attached to the arm of a computer-controlled pen motor. The muscle was stretched using various waveforms (steps, sine waves, white noise). The resulting spikes generated by the sensory neuron were measured using an extracellular electrode on the nerve. Neuromodulatory substances were introdueed to the preparation *via* switching ports in the superfusion system. A detailed description of the experimental setup and technique has previously been published (Birmingham *et al.*, 1999).

Modulation of a Stretch Receptor

I have discovered that the response of GPR2 to stretch can be modulated in two very different ways. In one case, the neuron's sensitivity can be continuously tuned through the application of several neuroactive substances. In the other case, an unknown internal mechanism drives the neuron between two qualitatively distinct modes of firing (Katz *et al.*, 1989; Birmingham *et al.*, 1999).

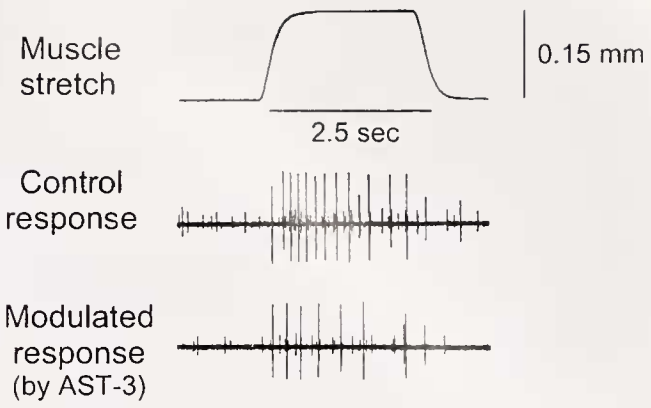

Figure 1. Stretch receptor response can be modulated by peptide application. Extracellular recordings of the activity of crab GPR2 neuron in control saline (middle) and in saline containing 10^{-8} *M* AST-3 (bottom) in response to stretch of the *cpv3a* muscle (top).

The sensitivity of the GPR2 response to muscle stretch can be modified by at least four distinct substances: serotonin, γ-aminobutyric acid (GABA), and the peptides TNRNFLRF-amide and allatostatin-3 (AST-3). I will focus on the effects of AST-3 in this paper. Figure 1 shows that the number of GPR2 spikes generated in response to muscle stretch is reduced in the presence of 10^{-8} *M* AST-3. The decrease in response is a continuous function of modulator concentration. The threshold for the AST-3 effect on firing rate is $10^{-9} - 10^{-8}$ *M*, and saturation occurs above 10^{-7} *M*. In most cases, the GPR2 stretch response is completely eliminated in 10^{-6} *M* AST-3.

Real sensory neurons have a maximum firing rate and thus a limited-amplitude dynamic range. Beyond the stretch amplitude corresponding to this rate, the neuron no longer is sensitive to additional stretch. One result of AST-3 application is to extend the dynamic range, as shown in Figure 2. Reduction in sensitivity causes the curve of rate *versus* stretch to be linearized. Large-amplitude stretches that were indistinguishable under control conditions can be differentiated in the modulator.

AST-3 application may also qualitatively change the feature detection capability of the GPR2 neuron. Figure 3 shows control and modulated responses to a *cpv3a* muscle stretch generated from filtered white noise. The corresponding muscle stretch velocity is shown beneath the spike trains. Under control conditions, the amplitude of the stretch is well described in the spike times (Birmingham *et al.*, 1999). In a high concentration (10^{-6} *M*) of AST-3, this is no longer the case. Many fewer spikes are generated, and it appears that those spikes might be correlated with large positive stretch velocities.

What is the effect of AST-3 application on the GPR2 code? More experiments are required to answer this question. One possibility is that AST-3 simply reduces the

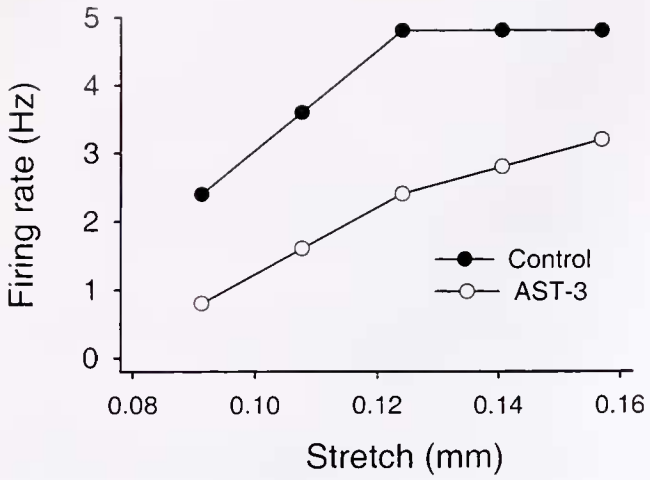

Figure 2. Neuromodulation can increase dynamic range. GPR2 firing rate as a function of *cpv3a* stretch amplitude in control saline and in saline containing 10^{-8} *M* AST-3.

sensitivity of GPR2 in a linear fashion, so that essentially the same features in the stimulus are being encoded as under control conditions. Far more interesting is the possibility that AST-3 changes the filtering properties of the neuron. The presence of the peptide might change GPR2 from what is basically a position detector into a sensor with a response that has a stronger dependence on muscle velocity.

GPR2 operates in two modes: the conventional "spiking" mode and a novel "bursting" mode (Katz *et al.*, 1989). In the spiking mode, which was the behavior shown in Figures 1–3, GPR2 generates spikes only during the stretch and is silent when not under tension. In contrast, in the bursting mode, GPR2 generates bursts of spikes (several seconds in duration) even when no stretch is imposed. In the initial description of the bursting mode, the average burst period was found to be ~17 s (Katz *et al.*, 1989). More recently, burst periods ranging between 12 and 101 s have been reported (Birmingham *et al.*, 1999). GPR2 can be driven from the spiking mode into the bursting mode though prolonged muscle activity (Birmingham *et al.*, 1999). The encoding properties of the neuron in the two modes are complementary. In the spiking mode, the neuron is best able to encode rapidly varying stretches, but not slower ones. In the bursting mode, fast stretches are ignored, while slower stretches (varying over minutes or hours) are encoded in the burst times (Birmingham *et al.*, 1999).

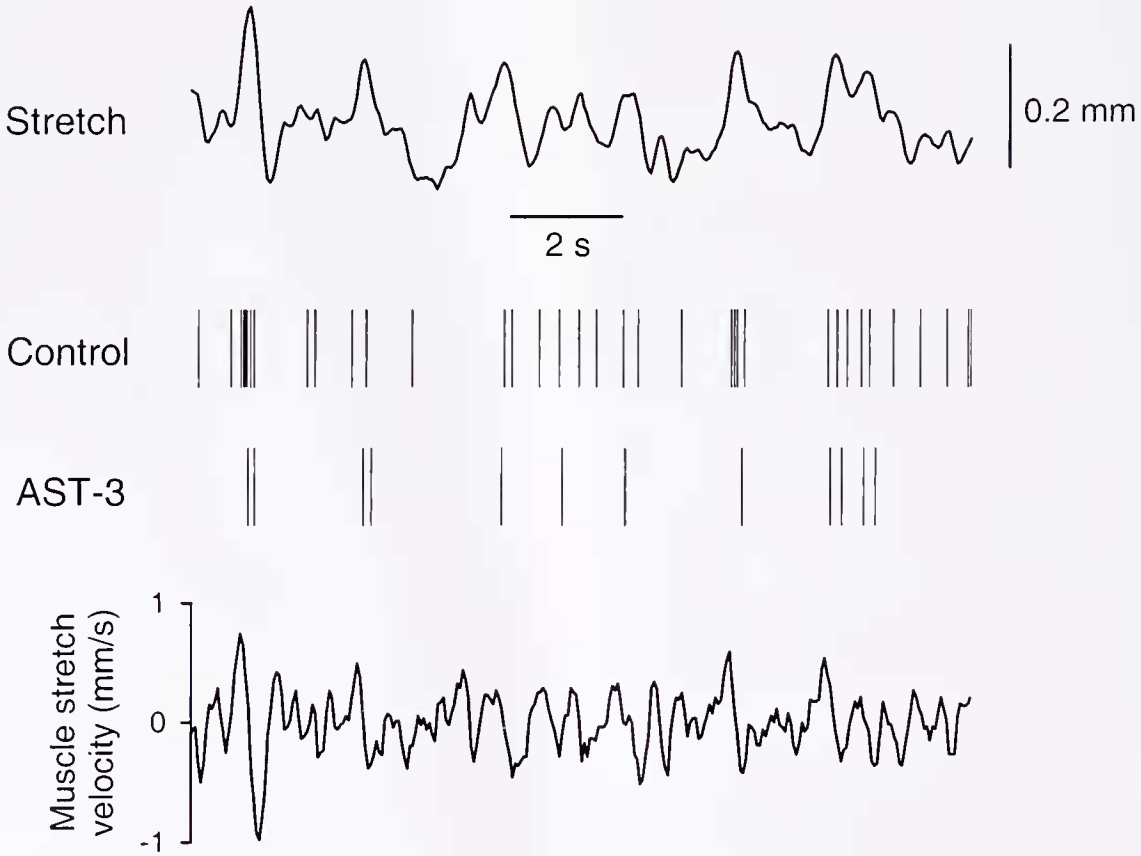

Figure 3. Neuromodulation may change a sensory neuron's filtering properties. GPR2 spikes in control saline and in 10^{-6} *M* AST-3 in response to *cpv3a* stretch generated from filtered white noise (top). Corresponding muscle stretch velocity is shown below the spike trains.

Pathways of Modulation of a Peripheral Sensor

At least three other neuromodulators, in addition to AST-3, affect GPR2 stretch response. Serotonin and GABA both decrease the response in a manner similar to that of AST-3. The peptide TNRNFLRF-amide, on the other hand, increases the neuron's spiking in response to a given stretch. Under what conditions GPR2 might be exposed to each of the various neuromodulatory substances remains unknown, but a hint is provided by immunohistochemical studies of the STNS. Both serotonin (Katz *et al.*, 1989) and an allatostatin-like peptide (Skiebe and Schneider, 1994) are contained within the GPR2 neuron itself. There have been no measurements yet made to determine whether either neuromodulator is released peripherally; however, since the stretch receptor both contains and responds to each substance, it is possible that GPR2 releases either or both to effect gain control through negative feedback. This would be similar to what has been observed in *Aplysia* bag cell neurons (Kauer *et al.*, 1987). The use of feedback to modify sensitivity in a crustacean stretch receptor has been previously reported for the lobster oval organ (Pasztor and Bush, 1989). They suggested that release of the peptide proctolin is used to activate a positive feedback loop that increased sensitivity to stretch. The activity-dependent switch from GPR2 spiking to bursting can likewise be viewed as feedback. We have confirmed that neither AST-3 nor serotonin can drive GPR2 into the bursting mode; the switching mechanism remains unknown and of great interest.

The GPR2 neuron does not contain GABA; however, there are GABA-containing neurons in the STNS whose axons project into the vicinity of GPR2 (Swensen *et al.*, 2000). Hence, GPR2 sensitivity might be modulated by instructions from another specific neuron in the nervous system. Peptides in the FLRFamide family have not been found in any of the cell bodies in the STNS but are known to circulate as hormones. Thus any GPR2 modulation by these substances would probably be accompanied by modifications of other elements in the nervous system.

Use of Adaptive Sensors in Robotic Applications

There are precedents for adaptive sensing in the field of artificial vision. "Active vision" schemes allow observer (robot) and sensor to interact continually (Blake and Yuille, 1992). The observer constantly changes its vantage point to allow the sensor to pick out the characteristics of images that are required to perform a task, while ignoring the rest. Strategies that allow economical data acquisition or handling are advantageous, especially with the development of high-resolution CCD cameras that generate huge amounts of data.

During the past decade, advances in chip design have resulted in the development of adaptive silicon photoreceptors (Delbruck and Mead, 1994). These sensors have high sensitivity and large dynamic range and were in part modeled after biological photoreceptors in the retina. They adjust their own sensitivities, without instructions from the central processor, in order to respond appropriately to changing environmental conditions. This is analogous to our model of how AST-3 and serotonin are used by GPR2. However, to the best of our knowledge, there are no robotic analogs to the GABA effect on GPR2, where the central processor sends instructions to a peripheral sensor to modify its response characteristics. This type of architecture might be useful in a smart robot. The sensor's performance could be adjusted for a given task in response to a command from the central processor or even from another sensor with a different modality.

Decoding the Signal From a Modulated Sensory Neuron

Modulation appears to give a sensory neuron the opportunity to be more flexible in its ability to encode different sorts of stimuli. However, the flip side of this flexibility, at least from the observer's point of view, is that there appears to be ambiguity in how a particular spike train should be interpreted. Two different sensory stimuli, encoded in two different neuromodulatory environments, could result in very similar neural signals. How is the apparent ambiguity in the "code" thus removed? This is a very general question that undoubtedly is an issue for most, if not all, sensory neurons, and the answer is not obvious. In the STNS this question is tractable because so many of the synaptic connections have been identified and characterized. GPR2 makes synapses onto many of the motor neurons in the CPG (Katz and Harris-Warrick, 1989, 1990), and so the postsynaptic responses to GPR2 spike trains can be directly measured using intracellular electrodes. It will be interesting to determine which features of the GPR2 spike train are important to the cells in the network, and if those are the same features we have identified in our mathematical decoding experiments.

We are well on our way to characterizing the encoding properties of the GPR2 neuron in its various modulated states. We are just beginning, however, to discover how GPR2 activity affects the output of the stomatogastric nervous system. Realistic GPR stimulation has been shown to initiate or modify specific motor programs (Katz and Harris-Warrick, 1989, 1990, 1991; Blitz and Nusbaum, 1996). In the STNS we can study how modulation of GPR2 affects the activity of individual targets as well as the output of the network, and we hope to discover how interactions between a CPG and a peripheral sensor can improve the performance of both sensor and network.

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Literature Cited

Birmingham, J. T., Z. B. Szuts, L. F. Abbott, and E. Marder. 1999. Encoding of muscle movement on two time scales by a sensory neuron that switches between spiking and bursting modes. *J. Neurophysiol.* **82:** 2786–2797.

Blake, A., and A. Yuille, eds. 1992. *Active Vision.* MIT Press, Cambridge, MA.

Blitz, D. M., and M. P. Nusbaum. 1996. Sensory neuron activation of modulatory projection neurons. *Soc. Neurosci. Abstr.* **22:** 1375.

CASSLS (The Center for Advanced Studies in the Space Life Sciences). 2001. Invertebrate sensory information processing: implications for biologically inspired autonomous systems. *Biol. Bull.* **200:** 145–245.

Delbruck, T., and C. A. Mead. 1994. Analog VLSI phototransduction by continuous-time, adaptive, logarithmic photoreceptor circuits. *CNS Memo #30.* Computation and Neural Systems Department, California Institute of Technology, Pasadena, CA 91125.

Foth, E., and D. Graham. 1983a. Influence of loading parallel to the body axis on the walking coordination of an insect. I. Ipsilateral effects. *Biol. Cybern.* **47:** 17–23.

Foth, E., and D. Graham. 1983b. Influence of loading parallel to the body axis on the walking coordination of an insect. II. Contralateral effects. *Biol. Cybern.* **47:** 149–157.

Grillner, S., and P. Wallen. 1977. Is there a peripheral control of the central pattern generators for swimming in dogfish? *Brain Res.* **127:** 291–295.

Kaczmarek, L. K., and I. B. Levitan. 1987. *Neuromodulation: The Biochemical Control of Neuronal Excitability.* Oxford University Press, New York.

Katz, P. S., and R. M. Harris-Warrick. 1989. Serotonergic/cholinergic muscle receptor cells in the crab stomatogastric nervous system. II. Rapid nicotinic and prolonged modulatory effects on neurons in the stomatogastric ganglion. *J. Neurophysiol.* **62:** 571–581.

Katz, P. S., and R. M. Harris-Warrick. 1990. Neuromodulation of the crab pyloric central pattern generator by serotonergic/cholinergic proprioceptive afferents. *J. Neurosci.* **10:** 1495–1512.

Katz, P. S., and R. M. Harris-Warrick. 1991. Recruitment of crab gastric mill neurons into the pyloric motor pattern by mechanosensory afferent stimulation. *J. Neurophysiol.* **65:** 1442–1451.

Katz, P. S., M. H. Eigg, and R. M. Harris-Warrick. 1989. Serotonergic/cholinergic muscle receptor cells in the crab stomatogastric nervous system. I. Identification and characterization of the gastropyloric receptor cells. *J. Neurophysiol.* **62:** 558–570.

Kauer, J. A., T. E. Fisher, and L. K. Kaczmarek. 1987. Alpha bag cell peptide directly modulates the excitability of the neurons that release it. *J. Neurosci.* **7:** 3623–3632.

Kawai, F., T. Kurahashi, and A. Kaneko. 1999. Adrenaline enhances odorant contrast by modulating signal encoding in olfactory receptor cells. *Nat. Neurosci.* **2:** 133–138.

Marder, E., and R. L. Calabrese. 1996. Principles of rhythmic motor pattern generation. *Physiol. Rev.* **76:** 687–717.

Maynard, D. M., and M. R. Dando. 1974. The structure of the stomatogastric neuromuscular system in *Callinectes sapidus, Homarus americanus* and *Panulirus argus* (Decapoda Crustacea). *Philos. Trans. R. Soc. Lond. B.* **268:** 161–220.

Pasztor, V. M., and B. M. W. Bush. 1989. Primary afferent responses of a crustacean mechanoreceptor are modulated by proctolin, octopamine, and serotonin. *J. Neurobiol.* **20:** 234–254.

Pearson, K. G., D. N. Reye, and R. M. Robertson. 1983. Phase-dependent influences of wing stretch receptors on flight rhythm in the locust. *J. Neurophysiol.* **49:** 1168–1181.

Skiebe, P., and H. Schneider. 1994. Allatostatin peptides in the crab stomatogastric nervous system: inhibition of the pyloric motor pattern and distribution of allatostatin-like immunoreactivity. *J. Exp. Biol.* **194:** 195–208.

Swensen, A. M., J. Golowasch, A. E. Christie, M. J. Coleman, M. P. Nusbaum, and E. Marder. 2000. GABA and responses to GABA in the stomatogastric ganglion of the crab *Cancer borealis. J. Exp. Biol.* **203:** 2075–2092.

Wilson, D. M. 1961. The central nervous control of flight in a locust. *J. Exp. Biol.* **38:** 471–490.